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Short Wave Ultraviolet Laser Energy in Porcine Coronary Arteries: Medial Cell Death and Neointimal Formation

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Background and Objective: **Smooth muscle cell migration and proliferation from arterial media into the neointima are major factors in the restenosis process following coronary angioplasty. Because short wave ultraviolet (UV) radiation is cytotoxic for rat carotid artery smooth muscle cells, the aims of this study were to determine the effects of short wave UV irradiation on normal pig coronary arteries and to evaluate the efficacy of UV laser energy for reducing neointimal hyperplasia (NI).**
Study Design/Materials and Methods: **In 13 pigs fed a normal diet, 37 coronary arteries were studied. UV laser light (275 nm) was applied in escalating doses from 0–16353 mJ/cm^2 via fiberoptic through a 20 mm PTCA balloon catheter. The pigs were euthanized at 21 days and histologic analysis performed. Arterial media was rendered acellular (ACM) in 20 of 33 irradiated coronary arteries (61%). The minimum UV energy density inducing ACM was 1348 mJ/cm^2. The fraction of acellular media to internal elastic lamina length (ACM/IEL) was 0.79 ± 0.29.**
Results: **No statistically significant difference was found between NI thickness at normal media sites (NM) vs. ACM sites (0.17 ± 0.14 mm vs. 0.16 ± 0.17 mm). No correlation was found between UV dose and NI formation (r = 0.307, *P* = 0.08).**
Conclusion: **Short wave UV irradiation induces ACM in normal porcine coronary arteries. Induction of acellular media is not associated with a reduction of NI formation in this porcine coronary model. Lasers Surg. Med. 21:374–383, 1997.**

Key words: coronary angioplasty; restenosis; vascular smooth muscle cell

INTRODUCTION

Coronary balloon angioplasty is a proven technique for treating coronary artery stenosis. However, restenosis remains a principal drawback of this procedure and occurs in ~30–40% of cases within 6 months [1–4]. The development of new interventional procedures has improved the immediate outcome but has not eliminated restenosis.

Smooth muscle cell migration and proliferation from the media into neointima is one of the dominant cellular events in the restenosis process [5,6], and strategies to limit neointima include killing medial smooth muscle cells. Short wave

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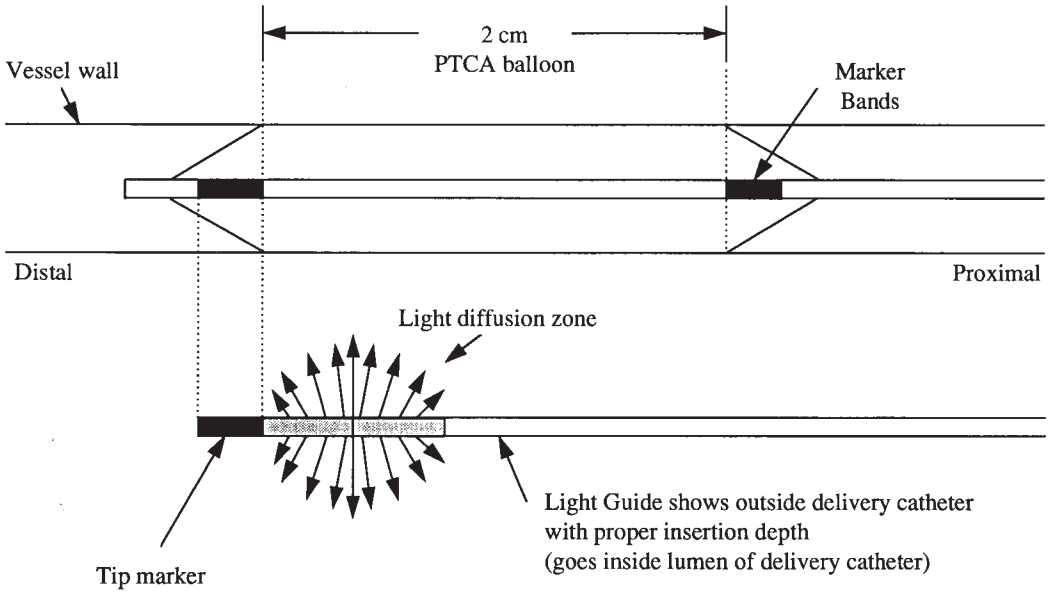

Fig. 1. Laser device. The sterile light guide conveys light from the light source to the delivery balloon catheter. It is inserted into the central lumen of the delivery catheter and positioned so that the light emanating from the end of the light guide exits through the balloon of the delivery catheter.

ultraviolet (UV) irradiation (266 nm) is cytotoxic for rat aorta vascular smooth muscle cells [7] and inhibits neointimal (NI) hyperplasia in balloon-injured rat carotid arteries [8]. Previous studies and clinical applications have used ultraviolet (UV) laser radiation of coronary arteries in ablative UV doses at considerably longer wavelength (308 nm) to remove atherosclerotic plaque [9–12]. The rationale of this experiment was, therefore, to evaluate the consequences of short wave UV energy on normal pig coronary arteries and vascular smooth muscle cells and to determine its effects on neointimal formation.

MATERIALS AND METHODS

Laser System

A Coherent® Innova® 400-25, continuous wave, 275 nm wavelength, 25 watt argon laser was used. The exposure duration was metered by a digital timing circuit. A sterile fiberoptic light guide conveyed the light from its source to the delivery balloon catheter. This guide was designed to fit through the central lumen of a standard PTCA balloon catheter modified to permit transmission of UV light. This catheter dispersed light within the balloon, and directed it toward the arterial wall (Fig. 1). Balloon diameters of 3.0 and 3.5 mm were used.

Animal Model

All studies were performed with the approval of the Mayo Foundation Institutional Animal Care and Use Committee. The pig model was used because the porcine coronary artery anatomy is comparable to humans, the coagulation system resembles humans, and direct histopathologic correlation with therapy is readily assessed.

Study Protocol

Thirteen domestic crossbred swine (Sus scrofa), (weight 20–30 kg) received premedication with aspirin 650 mg, ticlopidine 250 mg, and verapamil 120 mg the day before the procedure. Pigs were anesthetized with intramuscular ketamine (3 mg/kg) and xylazine (30 mg/kg). Continuous electrocardiographic and pressure monitoring were performed during the procedure. The left external carotid artery was surgically exposed and a 8 Fr arterial sheath introduced. Heparin (10,000 USP units) was administered intravenously as a bolus after sheath placement. The coronary artery was engaged using standard technique with an angioplasty guide catheter under fluoroscopic visualization.

Thirty-seven vessels received the UV laser energy. The delivery balloon size was either 3.0 mm or 3.5 mm at 2–4 atmospheres inflation pressure, chosen for a balloon:artery ratio of 1.1:1.

TABLE 1. Study Groups Characteristics

Group	No. arteries	Light guide	No. UV treatments at each site	UV dose (mJ/cm^2)	Injury
1	13	Stationary	1	0–16,002	No
2	12	Stationary	3	0–16,353	No
3	12	Moving	3	185–3,381	3 times 30% overdilatation
	Total = 37				

Vessel occlusion during balloon inflation was evaluated each time before laser treatment to confirm good apposition between the angioplasty balloon and vessel wall. The study groups are shown in Table 1. The first two study groups were performed to determine the baseline dose effect on the media and the effect of increasing UV energy on medial smooth muscle cells in vivo. For these studies, a stationary light guide was used with four different dose levels per group ranging from 0 to 16,002 mJ/cm^2 for group 1 and 0 to 16,353 mJ/cm^2 for group 2.

To test the potential of UV light for reducing NI formation (group 3), coronary arteries were injured with a 30% oversized balloon followed by irradiation using a moving light guide designed to cover the entire balloon length with UV energy. Delivered doses in this study ranged from 185 to 3,381 mJ/cm^2 due to technical variation in the delivery devices.

After the procedure, the carotid artery was ligated and the neck incision closed. The pigs were returned to the postoperative recovery area and were fed a standard diet without lipid or cholesterol supplementation.

Tissue Analysis and Data Processing

All animals were euthanized 21 days after the procedure using an intravenous commercial euthanasia solution by ear vein (Sleepaway, Fort Dodge Laboratories, 10 cc). Perfusion fixation was performed on the heart and coronary arteries. For each coronary artery, 24 tissue sections were cut transversely in 2 mm slices. Standard hematoxylin and eosin (H & E) and elastic van Gieson tissue stains were prepared. Quantitative histomorphometry measurements were obtained using a calibrated microscope, videoimaging system, and microcomputer program (JAVA, Jandel Scientific, Corte Madera, CA). All sections were stained with elastic van Gieson and manually traced with the following parameters measured: lumen area, area within the internal elastic lamina (IEL), IEL length, area within the external elastic lamina (EEL), and neointimal area and thickness. Neointima area in sections with intact IEL (*noninjured arteries*) was calculated as lumen area subtracted from the IEL area and for sections with IEL disruption (*injured arteries*), area between the lumen and the remnants of medial tissue or EEL. Medial area in sections with intact media was calculated as the area between the internal and external elastic laminae and for sections with IEL disruption, areas of remnants of medial tissue.

All sections were also stained with hematoxylin & eosin and evaluated for acellular media (ACM). This ACM was clearly visible as a pink band just outside the IEL devoid of cell nuclei (Fig. 2). To quantify the amount of this acellular media, each section with ACM was divided into four quadrants (Fig. 3). For each quadrant, the localization, length and thickness of ACM was measured. The following calculations were performed: (1) ratio of ACM/IEL length, or the fraction of IEL circumference occupied by ACM, (2) ratio of ACM/medial thickness, or the fraction of medial thickness that was rendered acellular, (3) relationship between laser dose and ACM/IEL length, (4) relationship between laser dose and ACM/medial thickness, and (5) NI thickness at each quadrant was measured and the mean NI thickness at ACM sites compared to the mean NI thickness at normal cellularity sites (NM). Mean NI thickness was also used to compare the NI thickness in relation to the fraction of the total circumference occupied by ACM.

Statistical Analysis

Linear regression and paired or unpaired t-tests were used when appropriate. Differences were considered significant when confidence limits exceeded 95% ($P < 0.05$). The results were expressed as mean ± SD.

RESULTS

Four coronary arteries that received no UV light (0.0 mJ/cm^2) for technical reasons were ex-

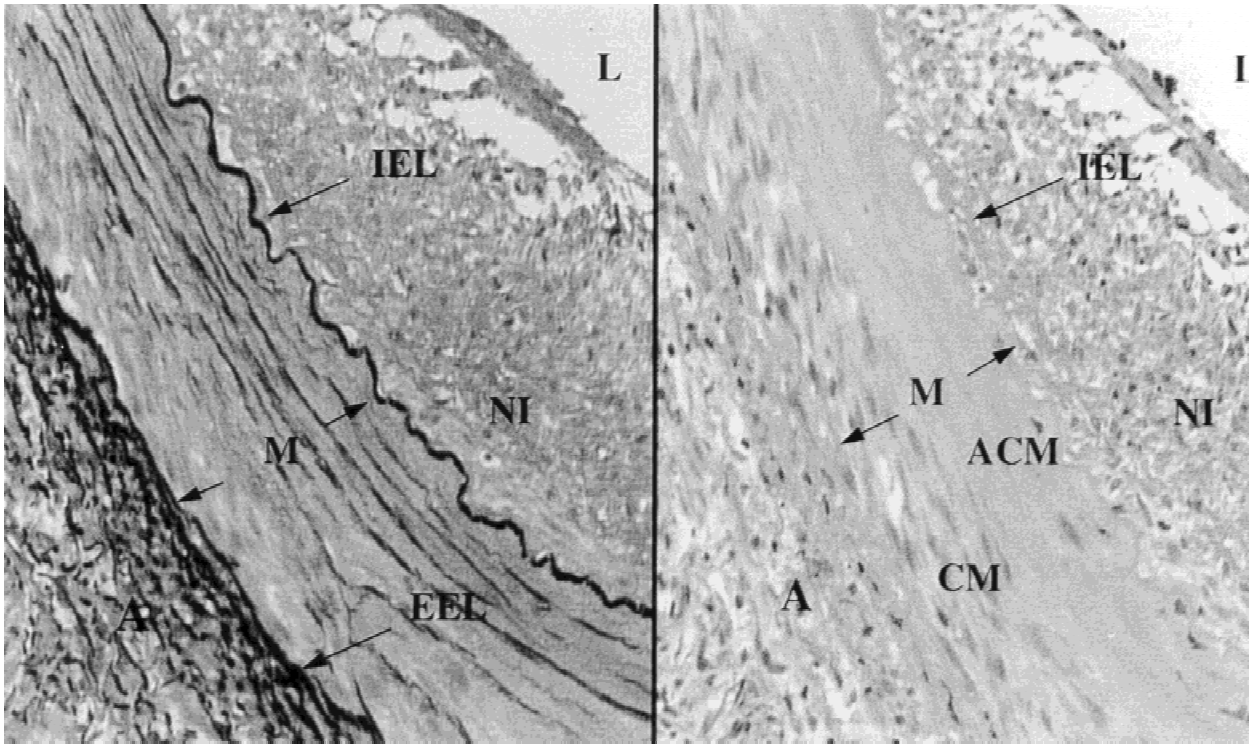

Fig. 2. Same histologic sections stained with Elastic van Gieson and Hematoxylin/Eosin of pig coronary artery 21 days after laser therapy. The pink acellular layer immediately adjacent to IEL and devoid of cell nuclei is acellular media induced by laser (elastic van Gieson and Hematoxylin/Eosin stain, magnification ×75).

cluded from analysis. Only coronary arteries that received short wavelength UV irradiation were included in the analysis. Acellular media was found in 20 of 33 irradiated coronary arteries (61%). The mean ratio ACM/IEL length was 0.79 ± 0.29, and the ratio ACM/medial thickness was 0.48 ± 0.17. The doses inducing ACM began at 1,348 mJ/cm^2 ranged to 16,353 mJ/cm^2, with a mean of 7,221 mJ/cm^2. There was a curvilinear correlation between dose and ACM/IEL length (Fig. 4), suggesting a threshold effect at ~5,000 mJ/cm^2. Above this dose no further increase of ACM length occurred. No relationship was found between UV dose and ACM/media thickness (Fig. 5) ($r = 0.028$, $P = 0.90$), and doses >5,000 mJ/cm^2 did not increase ACM thickness.

To determine the relationship between acellular media and neointimal formation. NI thickness was measured at ACM sites and compared to NI thickness at normal medial cellularity sites in the same section. The mean value for NI thickness at ACM sites was 0.16 ± 0.17 mm and NI thickness at normal media cellularity was 0.17 ± 0.14 mm ($P = 0.11$) (Fig. 6). In order to evaluate the relationship between ACM and NI thickness, we studied the arteries in which the ACM occupied one quadrant, 2 quadrants, 3 quadrants of the overall circumference (4 quadrants) vs. NI thickness (Fig. 7). No statistically significant difference was observed across groups with ACM (1/4 to 4/4) and NI thickness, and between all ACM groups and normal media group vs. NI thickness.

The effect of different UV doses on NI hyperplasia was studied and shown in Figure 8. No correlation was found between total NI (TNI) area per coronary artery (sum of the neointimal area at lesion sites for each vessel) vs. dose for injured ($r = 0.253$, $P = 0.36$) and noninjured arteries ($r = 0.196$, $P = 0.44$). Previous studies in porcine arteries demonstrate that vessel wall injury is required to stimulate neointimal growth, and no NI formation occurs in coronary arteries with intact IEL. We thus evaluated the effect of UV light at different doses on NI formation for injured and noninjured arteries. The relationship between high (>5,000 mJ/cm^2) and low (≤5,000 mJ/cm^2) UV dose (injured and noninjured coronary arteries) vs. mean NI area is shown in Figure 9. The raw data for TNI and dose are shown in Table 2. Statistically significant difference was found between injured TNI area low dose and noninjured

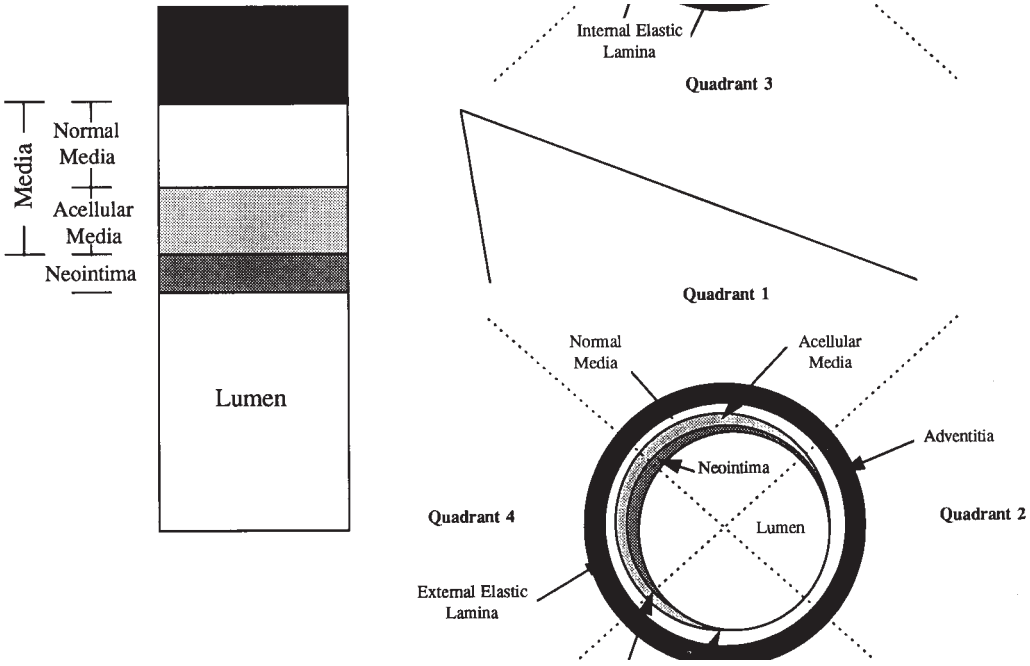

Fig. 3. Each section with acellular media was divided in four quadrants, and for each quadrant, the localization, length, and thickness of ACM was measured.

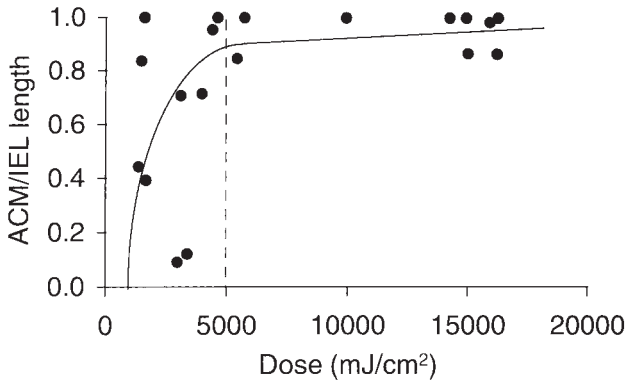

Fig. 4. Relationship of UV dose vs. ACM/IEL length. A curvilinear relationship was found. There was a dose threshold at ~5,000 mJ/cm^2, above which no increase of ACM length was found.

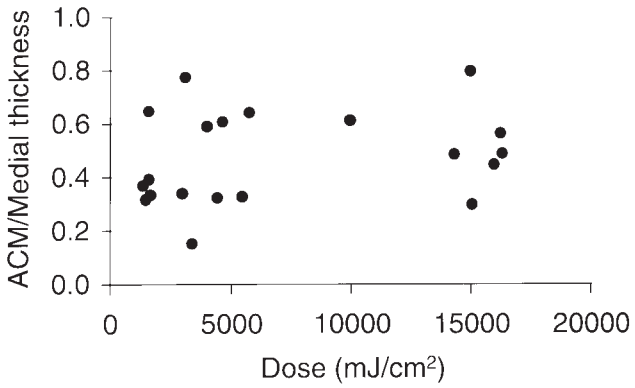

Fig. 5. Relationship of UV dose vs. ACM/Medial thickness. No relationship existed between dose and the ratio of media thickness. Doses above 5,000 mJ/cm^2 did not increase the thickness of ACM.

TNI area high and low UV doses ($P \leq 0.05$). The mean dose used for injured arteries (3,319.6 ± 5,257.1 mJ/cm^2) was significantly lower ($P = 0.03$) than the mean dose used for noninjured vessels 5,889 ± 5,691.4. UV radiation in uninjured coronary arteries clearly stimulated NI formation (area values from 2.09 to 8.15 mm^2 for noninjured arteries) (Fig. 8, Table 2). However, the neointimal hyperplasia area found in noninjured vessels was significantly less than injured arteries (3.31 ± 1.63 mm^2 vs. 7.20 ± 3.36 mm^2, $P = 0.03$).

DISCUSSION

To our knowledge, this is the first report of short wave ultraviolet laser energy applied to coronary arteries. The results showed that short wave ultraviolet light (275 nm) induces acellular

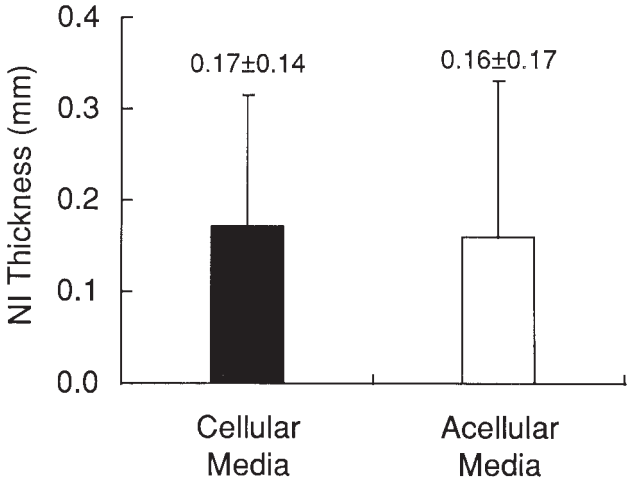

Fig. 6. Cellular and acellular media vs. NI thickness. No statistically significant difference was found between NI thickness at normal media cellularity sites vs. NI thickness at acellular media sites.

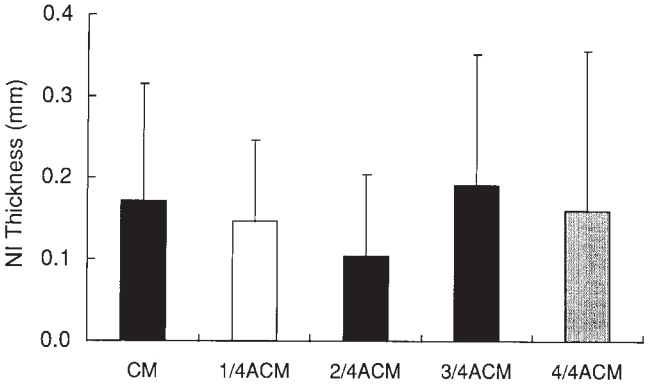

Fig. 7. Relationship between the fraction of the arterial circumference occupied by ACM vs. NI thickness. No statistically significant difference was found between each group of ACM regarding NI thickness and between the ACM groups and normal cellular media group vs. NI thickness. CM = cellular media, 1/4 ACM = 1/4 of the overall circumference occupied by ACM, 2/4 = half of the overall circumference occupied by ACM.

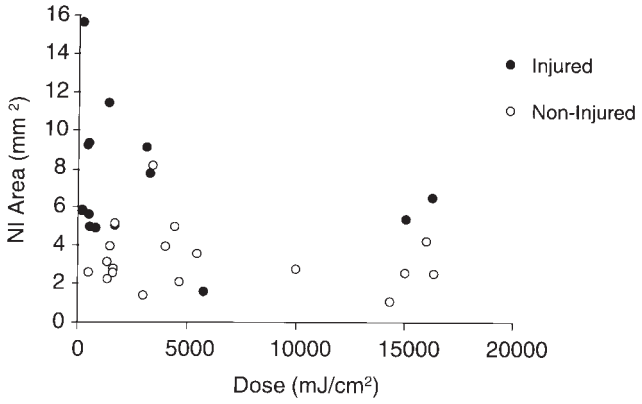

Fig. 8. Relationship between total neointimal area vs. dose for injured and noninjured arteries. This graph clearly demonstrates the stimulation of neointimal hyperplasia by UV light for noninjured arteries since no NI should be found in the absence of vessel wall damage.

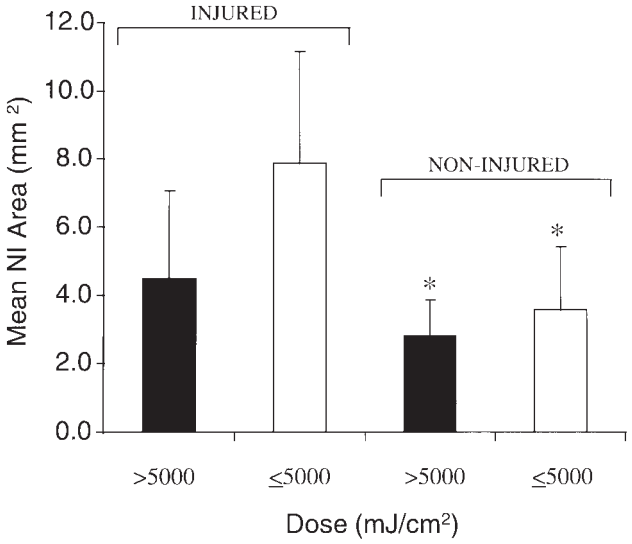

Fig. 9. Relationship between high and low UV dose (injured and noninjured coronary arteries) vs. mean NI area. A statistically significant difference was found between injured TNI area low dose and noninjured TNI area high and low dose (*$P \leq 0.05$).

media, similar to results in rat carotid arteries. Few studies describe the effects of short wave UV irradiation on vascular smooth muscle cell (VSMC). Clarke [7] investigated the effect of various laser irradiation wavelengths (UV, 266, 355 nm, visible, 532 nm, and infrared, 1,064 nm) on rat VSMC. Short wave UV energy (266 nm) had potent lethal effects, markedly limiting cells survival (0.01 vs. 1.03 control). Conversely, for longer wavelengths (355, 532, and 1064 nm), SMC mean surviving fractions (SF) were similar to control. In a recent study, Pastore et al. [8] used subablative UV light (262 nm) immediately following balloon injury of the rat common carotid artery. This device induced extensive medial necrosis in 4/11 treated arteries and significantly reduced intimal cross-sectional area, percent luminal narrowing, and intimal/medial area in the laser radiated group compared to control.

The mechanism of short wave UV light on tissue has been studied previously. The effect of far-ultraviolet laser on synthetic organic polymers [13] and on biological tissue [14–18] is reported to be "ablative photodecomposition," which results in the breakdown of intramolecular bonds

TABLE 2. Raw Data, Injured, and Noninjured Vessels, High and Low Doses

	Injured vessels				Noninjured vessels			
	>5,000 mJ/cm²		≤5,000 mJ/cm²		>5,000 mJ/cm²		≤5,000 mJ/cm²	
Dose	TNI (mm²)	Dose (mJ/cm²)	TNI (mm²)	Dose (mJ/cm²)	TNI (mm²)	Dose (mJ/cm²)	TNI (mm²)	Dose (mJ/cm²)
	6.5	16,290	7.74	3,268	2.53	16,353	2.09	4,641
	5.37	15,067	9.1	3,105	4.23	16,002	4.97	4,420
	1.59	5,761	5.03	1,672	2.57	15,027	3.94	3,990
			11.44	1,362	1.08	14,328	8.15	3,381
			4.89	804	2.76	9,980	1.4	2,972
			4.96	532	3.57	5,451	5.14	1,661
			5.6	489			2.78	1,600
			9.33	473			2.56	1,583
			9.21	423			3.95	1,461
			5.84	186			2.24	1,348
			5.78	185			3.13	1,324
			15.64	177			2.58	480
Mean	4.49	12,372.7	7.88	1,056.3	2.79*	12,856.8	3.58*	2,405.1
SD	2.57	5,758.4	3.27	1,097.6	1.07	4,292.1	1.84	1,401.5

*$P \leq 0.05$ TNI injured low dose vs. TNI noninjured high and low dose.

by direct action on the constituent molecules without thermal damage. The cytotoxicity and mutagenicity potential of 248 and 193 nm light has been described by Green et al. [19] in Chinese hamster ovary cells and in human diploid fibroblast lines. Excimer laser irradiation at 248 nm was more cytotoxic than 193 nm and induced mutation in proportion to dose. Laser irradiation at 193 nm did not cause mutations greater than the controls despite stronger absorption of DNA at this wavelength compare to 248 nm.

The essential role of SMC migration and proliferation in forming intimal hyperplasia after angioplasty has been extensively described [20–22]. In rat coronary arteries, SMC proliferation begins in the media about 24 hours after injury [23,24], and after 4 days, cells are readily observed on the luminal side of the internal elastic lamina. Hanke et al. [25], using an experimental rabbit model, revealed a peak of cells undergoing DNA synthesis within the first 7 days after angioplasty. SMC within the media underwent division later, and at 28 days proliferation in the media and intima reverted to low, normal levels. This proliferation process has been found in other species and is a nonspecific response of the arterial wall to many different types of injury. Additionally, a strongly positive correlation exists between the extent of injury and the intensity of the reparative response [26].

Because of the importance of the media in restenosis, elimination of cells in this structure has been the subject of many experiments. Thermal injury, external beam irradiation [26], or hyperinflation balloon injury [27] have all failed to reduce neointima in animal models. Our findings concur with those prior experiments. In this study, we induced acellular media in 61% of coronary arteries, yet found no correlation between acellular media and reduction of neointimal formation. Furthermore, no association was found between the circumferential magnitude of ACM and NI formation. ACM/IEL length correlated to ultraviolet dose, but no relationship was found between dose and the ratio of ACM/media thickness. This finding may be explained by the strong linear absorption of short wave ultraviolet energy by tissue and by the increased diffusion of light at higher doses. Technical problems with the device, such as radial nonuniformity, air bubbles, and film formation on the balloon by plasma protein, could have reduced the dose received to the vessel.

This study raises questions about the application of short wave UV light to normal, noninjured coronary arteries, since irradiated arteries without mechanical injury developed neointimal hyperplasia. We learned from previous studies that internal elastic lamina (IEL) disruption is *obligatory* for the induction of neointimal hyperplasia. Schwartz [26,28] and others [29–32] clearly demonstrated a strong and direct relationship between the extent of vessel wall injury and the degree of neointimal thickness (NI formation after IEL laceration alone < IEL + medial disruption < IEL + medial + adventitial lesion). Karas et al. [32] reported a significantly greater degree of neointimal hyperplasia after stenting than with oversize balloon angioplasty alone because the in-

tensity of vessel wall disruption after balloon overstretch only is more difficult to predict. These studies concluded that in the absence of IEL disruption, no neointimal hyperplasia, or a very minimal amount should be found. Although no relationship was demonstrated between dose and total NI area in our study (Fig. 8), short wave UV light obviously stimulated NI formation for noninjured arteries (area values from 2.09 to 8.15 mm^2) (Table 2). In our experiment, induction of ACM by UV laser induced NI formation in normal coronary arteries, yet failed to reduce neointimal hyperplasia in injured vessels. This result challenges the concept of SMC proliferation predominating in the restenosis phenomenon and suggests the important function of healthy media in intimal integrity. This concept is also supported by results from thermal injury (80°C for 30 seconds) on normal pig coronary arteries [33], where heat injury induced extensive medial necrosis, but neointimal hyperplasia always occurred at burn sites (α actin negative). Neointima was absent or minimal at α actin positive sites.

Limitations

There are certain limitations in this study. We used a nonatherosclerotic pig coronary arteries model, since there is little to no difference in the amount of NI formation of normal compared to hypercholesterolemic pigs. Grinstead et al. [34] compared the degree and nature of coronary neointimal thickening between three different porcine restenosis models: endothelial abrasion-hypercholesterolemic diet-stenting, hypercholesterolemic diet-stenting, and stenting alone. No difference was found regarding neointimal thickening or the predominant cellular content and collagen matrix in each model. In this study, stent implantation alone appears to be the major stimulus for neointimal hyperplasia. Schneider et al. [35] showed no difference in neointimal thickness between overstretch balloon injury alone and balloon injury associated with hypercholesterolemic diets. These studies and others [36,37] implied a less important role for cholesterol feeding in neointimal formation after vessel wall injury in pigs and explained the use of overstretch injury alone in our experiment. Moreover, the well-documented proportional neointimal response to coronary artery injury using balloon angioplasty alone or after stenting has been extensively described previously [26,28,30–32]. Consequently, we did not include a control group in our study, but instead refer to the literature.

The variability in the distribution of ACM demonstrated in our study could be partially explained from bench experiments and theoretical analysis. When the inner shaft of the balloon catheter is off-center and in contact with the wall of the balloon, the minimum dose on the opposite vessel wall can be ~50% less than if the inner was centered in the balloon. We were unable to measure the degree of radial nonuniformity during UV delivery. The maximum dose may be as much as five times greater where the inner contacts the balloon wall than if the inner were centered. A better design of the delivery catheter should improve the centering of laser light within the balloon.

Finally, although a statistically significant difference was found between injured TNI area low dose and noninjured TNI area high and low dose, some limitations should be addressed regarding this conclusion: (1) the absence of significant UV effect on NI formation for all treated groups was demonstrated by the increase of NI area at higher dose for the high dose group and the absence of any correlation between dose and NI area for the other groups, and (2) the small number of observations for the injured high dose group and the extreme variation of TNI area found in the injured low dose group (related to the level of vessel wall injury) vs. the noninjured groups could have amplified the statistical differences.

Conclusion

Restenosis after coronary angioplasty is a complex and incompletely understood biological phenomenon. Theoretically, because the vascular smooth muscle cells play an essential role in the restenosis process, killing medial smooth muscle cells should reduce migration and proliferation and thus neointimal formation. Our study indicates precisely the opposite, namely, that inducing acellular media with short wave ultraviolet irradiation in swine coronary arteries does not reduce neointima formation. These findings support an incomplete understanding of neointimal hyperplasia and suggest that the paradigm of killing medial SMC may not solve the clinical restenosis problem.

ACKNOWLEDGMENTS

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REFERENCES

1. Serruys PW, Luijten HE, Beat K, Geuskens R, de Feyter P, van den Brand M, et al. Incidence of restenosis after succesful coronary angioplasty: a time-related phenomenon: a quantitative angiographic study in 342 consecutive patients at 1,2,3, and 4 months. Circulation 1988; 77:361–371.
2. Liu MW, Roubin GS, King SB. Restenosis after coronary angioplasty: Potential biologic determinants and role of intimal hyperplasia. Circulation 1989; 79:1374–1387.
3. Nobuyoshi M, Takeshi K, Ohishi H, Horiuchi H, Nosaka H, Hamasaki N, Yokoi H, Kim K. Restenosis after percutaneous transluminal coronary angioplasty: Pathologic observation in 20 patients. J Am Coll Cardiol 1991; 17: 433–439.
4. Califf RM, Fortin DF, Frid DJ, Harlan III WR, Ohman EM, Bengtson JR, et al. Restenosis after coronary angioplasty: An overview. J Am Coll Cardiol 1991; 17(6):2B–13B.
5. Ip JH, Fuster V, Badimon J, Taubman MB, Chesebro JH. Syndromes of accelerated atherosclerosis: Role of vascular injury and smooth muscle cell proliferation. J Am Coll Cardiol 1990; 15:1667–1687.
6. McBride W, Lange RA, Hillis LD. Restenosis after successful coronary angioplasty. NEJM 1988; 318:1734–1737.
7. Clarke RH, Isner JM, Van Tassel R. Wavelength-dependent cytotoxicity of laser light on vascular smooth muscle: Implications for restenosis prevention [abstract]. Circulation 1991; 84:II–360.
8. Pastore CJ, DeJesus ST, Van Tassel RA, Holmes DR, Schwartz RS, Clarke RH, Isner JM. Low dose, subablative ultraviolet (UV-C) laser irradiation from a Q-switched, frequency-quadrupled Nd:YLF diode laser inhibits neointimal hyperplasia in balloon-injured rat carotid arteries [Abstract]. J Am Coll Cardiol 1994:472A.
9. Grundfest WS, Litvack F, Forrester JS, Goldenberg T, Swan HJC, Morgenstern L, et al. Laser ablation of human atherosclerotic plaque without adjacent tissue injury. J Am Coll Cardiol 1985; 5(4):929–933.
10. Grundfest WS, Litvack F, Goldenberg T, Sherman T, Morgenstern L, Carroll R, et al. Pulsed ultraviolet lasers and the potential for safe laser angioplasty. Am J Cardiol 1985; 150:220–226.
11. Litvack F, Eigler NL, Margolis JR, Grundfest WS, Rothbaum D, Linnemeir T, et al. Percutaneous excimer laser coronary angioplasty. Am J Cardiol 1990; 66(15):1027–1032.
12. Marmur JD, Sanborn TA, Kahn H, Badimon JJ, Badimon L, Fuster V. Acute biologic response to excimer versus thermal laser angioplasy in experimental atherosclerosis. J Am Coll Cardiol 1991; 17(4):978–984.
13. Srinivasan R. Ablation of polymers and biological tissue by ultraviolet lasers. Science 1986; 234:559–565.
14. Bowker TJ, Cross FW, Rumsby PT, Gower MC, Rickards AF, Bown SG. Excimer laser angioplasty: Quantitative comparison in vitro of three ultraviolet wavelengths on tissue ablation and haemolysis. Lasers Med Sci 1986; 1: 91–99.
15. Deckelbaum LI, Isner JM, Donaldson RF, Clarke RH, Laliberte SM, Aharon AS, Salem DN. Excimer laser irradiation of cardiovascular tissues: standardized comparison of 193, 248, 308, and 351 nm wavelengths. [Abstract]. Circulation 1985; 72:IIII–372.
16. Grundfest WS, Litvak F, Forrester JS, Fishbein M, Morgenstern L. Pulsed ultraviolet lasers provide precise control of atheroma ablation [Abstract]. Circulation 1984; 70:II–35.
17. Isner JM, Aharon AS, Donaldson RF, Deckelbaum LI, Clarke RH. Excimer laser irradiation of cardiovascular tissue in blood and fluosol [Abstract]. Circulation 1985; 72:III–457.
18. Linsker R, Srinivasan R, Wynne JJ, Alonso DR. Far-ultraviolet laser ablation of atherosclerotic lesions. Lasers Surg Med 1984; 4:201–206.
19. Green H, Boll J, Parrish JA, Kochevar IE, Oseroff AR. Cytotoxicity and mutagenicity of low intensity, 248 and 193 excimer laser radiation in mammalian cells. Cancer Res 1987; 47:410–413.
20. Austin GE, Ratliff NB, Hollman J, Tabei S, Phillips DF. Intimal proliferation of smooth muscle cells as an explanation for recurrent coronary artery stenosis after percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1985; 6:369–375.
21. Casscells W. Migration of smooth muscle and endothelial cells. Critical events in restenosis. Circulation 1992; 86: 723–729.
22. Clowes AW, Clowes MM, Fingerle J, Reidy MA. Regulation of smooth muscle cell growth in injured artery. J Cardiovasc Pharmacol 1989; 14(Suppl. 6):S12–S15.
23. Clowes AW, Reidy MA, Clowes MM. Kinetics of cellular proliferation after arterial injury: I. Smooth muscle growth in the absence of endothelium. Lab Invest 1983; 49:327–333.
24. Reidy MA, Fingerle J, Lindner V. Factors controlling the development of arterial lesions after injury. Circulation 1992; 86(suppl III):III-43–III-46.
25. Hanke H, Strohschneider T, Oberhoff M, Betz E, Karsch KR. Time course of smooth muscle cell proliferation in the intima and media of arteries following experimental angioplasty. Circ Res 1990; 67:651–659.
26. Schwartz RS, Huber KC, Murphey JG, Edwards WD, Camrud AR, Vlietstra RE, Holmes DR. Restenosis and the proportional neointimal response to coronary artery injury: Results in a porcine model. J Am Coll Cardiol 1992; 19:267–274.
27. Van Erven L, Post MJ, Velema E, Borst C. In the normal rabbit femoral artery increasing arterial wall injury does not lead to increased intimal hyperplasia. J Vasc Res 1994; 31:153–162.
28. Schwartz RS, Murphy JG, Edwards WD, Camrud AR, Vlietstra RE, Holmes DR. Restenosis after balloon angioplasty: A practical proliferative model in porcine coronary arteries. Circulation 1990; 82:2190–2200.
29. Wollberg SC, Minor ST, Smith GS, Rodgers GP, Mims M, Guyton JR. Intracoronary stenting accelerates luminal narrowing in hypercholesterolemic swine [Abstract]. Circulation 1990; 82((suppl III)):III-656.
30. Rodgers GP, Minor ST, Robinson K, Cromeens D, Stephens LC, Woolbert SC, et al. The coronary artery response to implantation of a balloon-expandable flexible stent in the aspirin- and non-aspirin-treated swine model. Am Heart J 1991; 122:640–647.

31. Rodgers GP, Minor ST, Robinson K, Cromeens D, Woolbert SC, Stephans LC, et al. Adjuvant therapy for intracoronary stents: Investigations in atherosclerotic swine. Circulation 1990; 82:560–569.
32. Karas SP, Gravanis MB, Santoian EC, Robinson KA, Anderberg KA, King SB. Coronary intimal proliferation after balloon injury and stenting in swine: An animal model of restenosis. J Am Coll Cardiol 1992; 20(2):467–474.
33. Schwartz RS, Edwards WD, Huber KC, Antoniades LC, Bailey KR, Camrud AR, Jogerson MA, Holmes Jr, DR. Coronary restenosis: prospects for solution and new perspectives from a porcine model. Mayo Clin Proc 1993; 68:54–62.
34. Grinstead WC, Rodgers GP, Mazur W, French BA, Cromeens D, Van Pelt C, West SM, Raizner AE. Comparison of three porcine restenosis models: The relative importance of hypercholesterolemia, endothelial abrasion, and stenting. Coronary Artery Dis 1994; 5:425–234.
35. Schneider JE, Santoian EC, Gravanis MB, Cipolla G, Anderberg K, King SBR. Lovastatin fails to limit smooth muscle cell proliferation in normolipemic and hyperlipemic swine in an overstretch balloon injury model of restenosis [Abstract]. J Am Coll Cardiol 1992; 19:162A.
36. Griggs RT, Bauman RW, Reddick RL, Read MS, Koch GG, Lamb MA. Development of coronary atherosclerosis in swine with sever hypercholesterolemia. Lack of influence of von Willebrand factor or acute intimal injury. Atherosclerosis 1986; 6:155–165.
37. Weiner BH, Ockene IS, Levine PH, Cuenoud HF, Fisher M, Johnson BF, et al. Inhibition of atherosclerosis by codliver oil in a hyperlipidemic swine model. N Engl J Med 1986; 315:841–846.